

Letter from the editor

Is combination treatment best for depression in adolescents?

Context: An estimated 5% of adolescents meet the criteria for major depressive disorder, with suicide related events occurring in up to 50% of these.[1] Despite this, either because of concerns about the safety of antidepressants in young people, or the failure to distinguish normal adolescent mood swings from a serious depressive disorder, such adolescents frequently receive supportive care only.

The Treatment for Adolescents with Depression Study (TADS), first published in 2003, investigated the effects of cognitive behavioural therapy (CBT) either alone or in combination with fluoxetine, a selective serotonin reuptake inhibitor (SSRI) antidepressant, in adolescents with major depression. The December 2006 issue of the *Journal of the American Academy of Child and Adolescent Psychiatry* featured a section devoted to in-depth reports of the TADS, which we discuss here.

Summary: The TADS study, funded by the National Institute of Mental Health in the USA, randomised 439 adolescents aged 12–17 years with major depression, an IQ of 80 or more, and limited additional comorbidity, to one of four treatment groups: fluoxetine alone (10–40 mg daily); CBT alone (15 sessions); combined fluoxetine plus CBT; and pharmacological placebo alone. All treatments continued for 12 weeks, at which time primary outcomes were assessed (changes in the scalar Children’s Depression Rating Scale-Revised (CDRS-R) total score, remission taken as CDRS-R score of 28 or less; and responder status, defined as much improved or very much improved on the Clinical Global Impressions–Improvement Scale).

Findings: After 12 weeks, combination treatment was found to be as effective as, or more effective than, other active treatments as measured by the primary outcomes,[2] and time to response.[3] In addition, the investigators reported higher suicide related events in the fluoxetine only group compared with the combined treatment group (9.2% with fluoxetine compared with 4.7% with combination treatment, 4.5% with CBT and 2.7% with placebo; P = 0.04 for fluoxetine compared with placebo).[5] The number needed to treat (NNT) for one adolescent with major depression to have a good outcome as measured by CGI-I score is shown for each group in the table.[1]

	Combination N = 107	Fluoxetine alone N = 109	CBT alone N = 111	Placebo N = 112
Remission rate at 12 weeks	37%	23%	16%	17%
P value for comparison with combination therapy		0.02	0.0004	0.0009
NNT (95% CI) compared with placebo	3 (2–4)	4 (3–8)	12 (5–23)	

Appraisal: The TADS study has been described as ‘...the most sophisticated clinical trial ever conducted in youth with internalising disorders’.[1] However the trial design has several important limitations.

- No psychological placebo was used but, as the investigators state, sham psychosocial treatments are only credible if they have some effect – which means that they may not be considered truly sham.

- The trial recruitment criteria excluded any adolescent who had failed two or more treatment episodes with SSRIs or with CBT, which may reduce the external validity of the investigators' findings.
- The adolescents included in the study had more severe depression than those included in previous studies. At recruitment, half had psychiatric co-morbidity, and one quarter had been suspended or excluded from school. However, the investigators claim that the characteristics of their participants reflected those of adolescents who present with depressive disorder in the general population, and therefore that their results are likely to be generalisable to the wider population of American youth.[1]
- Only one drug was studied in the TADS, raising questions about the generalisability of the study to other SSRIs and antidepressant groups.
- Finally, the TADS investigators report the 12 week follow up data only, when the original study also performed a 36 week follow up. Reporting the final outcomes would provide important information on long term efficacy and relapse rates for the different treatments.

In summary, combined treatment with CBT plus fluoxetine was more effective for the primary outcomes than either treatment alone, or placebo. However, the benefits of the treatments provided within the study do not hide the fact that, even after 12 weeks of treatment, less than one quarter of adolescents were in remission. There have been serious concerns that SSRIs may increase suicide risk. In this study fluoxetine alone, but not CBT plus fluoxetine, was associated with an increase in suicide related events. If there is one take-home message for clinicians from The Treatment for Adolescents with Depression Study, it must be that for adolescents diagnosed with major depression, doing nothing is no longer an acceptable option.

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